REMARKS

With the filing of this RCE, Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

I. Introduction

Claims 8 and 12 were cancelled previously. Pending claims 1 and 35-37 are amended. Withdrawn claim 15 is also amended. The word "stable" and the phrase "free from biological contaminants" or iteration thereof was added to the amended claims. Support for this amendment is found at page 18, under heading "4. Sterile Filtration." No new matter is added.

The amendment of "free from biological contaminants" is a recited element of the claim. This element is further defined by a functional limitation: the dispersion must be capable of sterilization be passing it through a filter having a pore size of 0.2 μm or less.

A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. As in the present claims, a functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step. *In Innova/Pure Water Inc. v. Safari Water Filtration Sys. Inc.*, 381 F.3d 1111, 1117-20 (Fed. Cir. 2004). One example in the chemical arts is found in *In re Barr*, 444 F.2d 588 (CCPA 1971) (A limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent" although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought.)

Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 1-7, 9-11 and 13-37 will be pending, with claims 15-34 withdrawn from consideration.

II. Rejection of Claims under 35 U.S.C. §103(a)

The Examiner and Applicants are at odds over what conclusion can be drawn from the teaching of Desai. The Examiner cites to Desai (and now to US Patent No. 6,139,870[1]) as supporting the general knowledge in the art that if dispersions contain particles smaller than 200 nm, it is obvious to one of ordinary skill in the art that they can be sterile filtered. Office Action at page 10 and 11 ("In order for any dispersions to go through the said filters, the particle size has to be at or less than 0.2 microns.") Applicants contend that such a statement, although seemingly logical, would not be the conclusion that one of ordinary skill in the art would draw when reading Desai (or that of the '870 patent which is mentioned but not used to support he rejection).

Applicants disagree that one of ordinary skill in the art would make such an expansive conclusion from Desai in view of A) the misinterpretations of Desai along with the limited examples, and B) the unpredictability in the art evidenced by the failed examples in the present specification.

A. Desai does not Provide Sufficient Teachings to Support the Examiner's General Conclusion

The Examiner cites Desai to support the general statement that particles smaller than 0.2 microns can be sterilized by filtration.

To reach this conclusion, one of ordinary skill in the art must ignore critical teachings of Desai. First, one must ignore that Desai distinguishes and clearly defines what he means by a surfactant and a surface stabilizing agent. Second, with this distinction by Desai in mind, one must also consider that Desai provides only one example, a protein-bound isoreserpine particle.

[1] US Patent No. 6,139,870 is not cited in the rejection. It appears to be used only in support of the Examiner's general statement. The '870 patent discloses a liquid water and oil emulsion and uses the term "particles" to describe the oil droplets. Liquid droplets are not germane to sterile filtration of solid particles.

When one skilled in the art reads Desai for all that it teaches, a general conclusion that all dispersions having particles smaller than 0.2 μm can be sterilized by filtration is not supported.

1. Desai Distinguishes and Clearly Defines what is Meant by a Surfactant and a Surface Stabilizing Agent

One of ordinary skill in the art would read Desai for all that it teaches, and that which it does not, before making a general statement about the art based upon Desai. When this exercise is properly done, one skill in the art would not expand the limited teachings of Desai to support the Examiner's general statement that all dispersions containing particles smaller than 200 nm can be sterilized by filtration.

The Examiner has taken the teachings of Desai out of context two times at page 8 of the Office Action. First, in support of the Examiner's general statement, the Examiner alleges that Desai teaches one of ordinary skill in the art that filtration can be used with any surface stabilized particle. At line 7, the Examiner states: "Desai also teaches that other surfactants and stabilizing agents are added to the particles." Second, in support of the Examiner's general statement, the Examiner alleges that Desai teaches one of ordinary skill in the art that to use the same surfactants and co-surfactants as that of Applicants' invention. At the second full paragraph of page 8: "Desai et al teach that nanoparticles of active agents and co-surfactants can be produced," citing to paragraphs [0094]-[0100] and then to paragraphs [0271]-[0295] to identify which suitable surfactants Desai contemplated. These cited paragraphs are taken out of context and do not support the Examiner's conclusion about the teachings of Desai.

First, Desai does not teach that other surfactants and stabilizing agents are added to the particles. To the contrary, Desai distinguishes his use of the protein albumin as a surface stabilizer from the prior art's use of "common" surfactants and surface stabilizing agents (e.g., Tweens and Pluronics). To this point, at paragraph [0163] Desai states: "unlike conventional methods for nanoparticle formation, no surfactant (e.g., sodium lauryl sulfate, lethicin, tween 80, pluronic F-68, and the like) is added to the mixture." (emphasis added).

Second, Desai differentiates the use of his surfactants and co-surfactants from the use of surfactants and co-surfactants as surface stabilizers. Paragraphs [0094]-[0100] of Desai use the terms "surfactant" and "cosurfactant." For one of ordinary skill in the art to understand what Desai meant by those terms, one would be led to paragraphs [0271]-[0295] (cited by the Examiner). Paragraph [0271] defines a surfactant as "capable of spontaneously forming oil-in-water microemulsions, in the presence of suitable cosurfactant and solvent." Exemplary surfactants include the Tweens and Pluronics. A teaching of a compound that is capable of spontaneously forming oil-in-water microemulsions (i.e., the function of a surfactant as defined by Desai) would not lead one of ordinary sill in the art to use such a compound as a surface stabilizer (which is how the Examiner needs them to be used to support the general statement). Because Desai clearly identifies the function of his "surfactants," one of ordinary skill in the art would not read Desai to support the use of these "surfactants" as surface stabilizers.

The two-above citations to Desai's "surfactants" are taken out of context and fail to support the Examiner's expansive interpretation that Desai supports the general statement that particles smaller than 200 nm can be sterilized by filtration.

2. The Only Working Example in Desai is a Protein-bound Isoreserpine Particle

The only working examples which Desai sterilized by filtration includes a single drug bound by protein. Desai only discloses a single dispersion (Example 8 and repeated in Example 9) of isoreserpine particles with albumin-bound protein. The Examiner reads Desai's specification as allowing the use of other active agents and other surface stabilizers in support of the general statement that all nanoparticles less than 200 nm can be sterilized by filtration.

As discussed above, Desai does not teach the interchangeability of the albumin with conventional surface stabilizers. In fact, he distinguishes them from albumim. Therefore, Desai cannot be read to support a statement that non-protein bound particles can also be sterile filtered.

One of ordinary skill in the art would not expand a disclosure of one working example to support the Examiner's general statement. Although Desai does provide a laundry list of other active ingredients contemplated by his invention, the only working active agent example is isoreserpine. Desai has not identified that isoreserpine shares a common feature or attribute with the other contemplated active ingredients which feature would allow one of ordinary skill in the art to draw some conclusion that the other active ingredients listed could form particles in the same manner as isoreserpine. Nor has Desai provided alternative methods of making other active-ingredient containing particles with albumin as a surface stabilizer to provide one of ordinary skill in the art the predictability that substitution of one of Desai's other listed active agents would perform the same as isoreserpine.

Considering Desai does not teach the interchangeability of the albumin with a "conventional" surface stabilizer and the lack of teaching to one skilled in the art to substitute another active agent for isoreserpine, Desai does not support the general statement that any active agent nanoparticle can be made, and successfully sterile filtered if it has a particle size less than 200 nm.

B. Applicants' Examples are Evidence of the Unpredictability in the Art

Applicants argued that the Examples in the specification demonstrate the unpredictability in the art of sterile filtering nanoparticulate dispersions. Such evidence directly contradicts the Examiner's conclusion that Desai can be read as a general teaching that as along as the particles in a dispersion are smaller than 0.2 μm, they can be sterilized by filtration.

The table below summarizes the results presented in the working examples of the specification.

Example	Active Agent	Surface Stabilizer	Particle Size	Sterile Filtration
1	budesonide	tyloxapol	80 nm	Yes
2	budesonide	tyloxapol and Hydroxypropylmethyl cellulose (HPMC)	90 nm	Yes
3	budesonide	Tyloxapol	80 nm	Yes
4	budesonide	tyloxapol and PVP	80 nm	Yes
5	budesonide	Hydroxypropylmethyl cellulose (HPMC)	89 nm	No
6	budesonide	methyl cellulose	2 microns	No
7	budesonide	Pluronic® F108	276 nm	No
8	budesonide	polysorbate 80	192 nm	No
9	budesonide	polysorbate 80 and polyvinyl pyrrolidone (PVP)	203 nm	No
10	beclomethasone	tyloxapol and polyvinyl pyrrolidone (PVP)	97 nm	Yes
11	beclomethasone	Tyloxapol	98 nm	Yes
12	beclomethasone	polysorbate 80	241 nm	No
13	beclomethasone	polysorbate 20	193 nm	No
14	beclomethasone	PVP	387 nm	No
15	flunisolide	Tyloxapol	99 nm	No
16	triamcinolone acetonide	Tyloxapol	157 nm	No
17	triamcinolone acetonide	Tyloxapol	144 nm	No
18	triamcinolone acetonide	tyloxapol and polyvinyl pyrrolidone (PVP)	117 nm	No

As demonstrated by Examples 5, 8, 13, 15, 16, 17 and 18, although a nanoparticulate dispersion having an effective average particle size of less than 200 nm can be obtained, the dispersion cannot be sterilized by filtering through a 0.22 micron filter due to aggregation or other factors. This is itself evidence of the unpredictability in the art of forming stable nanoparticulate dispersions, discussed in more detail below. Accordingly, Applicants have established that there is unpredictability in the art concerning a nanoparticulate dispersion that can be sterile filtered with a filter having a pore size of 0.2 μm or less.

At page 9 of the Office Action, the Examiner concludes that the Examples show that if the dispersion contains particles smaller 200 nm in diameter, they can be successfully sterile filtered; and those that contain particles larger than 200 nm cannot. (This statement first assumes that obtaining stable nanoparticulate dispersions is predictable.) With this view, the Examiner then dismisses Applicants' examples that report a particle size over 200 nm or that aggregated. What remains, according to the Examiner's analysis, are the successfully filtered dispersions (Examples 1-4, 10 and 11) and the one, unexplained failure (Example 15). The Examiner concludes at page 9 that "one unexplainable set of data is not support[ive] of unpredictability (1 out of 18)."

The Examiner's analysis of the Examples is incorrect. If the Examples that did not produce a dispersion having a stable particle size less than 200 nm are dismissed, they cannot be used to show predictability. (What these Examples demonstrate is the unpredicatability of forming stable nanoparticluate dispersions.) The Example pool therefore is not all 18 Examples, but is limited to the Examples showing a stable dispersion having a particle size of less than 200 nm, i.e., Examples 1-4, 10, 11, and 15. Thus the "odds" of predictability are 6 out of 7, not 17 out of 18. This may appear like the event is more predictable, but it ignores critical prior events.

A 6 out of 7 "odds" ignores the fact that one of ordinary skill in the art would consider how likely it is in the first instance to even obtain a stable dispersion having particles of less than 200 nm in size. The Examples show the "odds" of successfully obtaining a dispersion with

particles less than 200 nm in size is 14 out of 18 (78%). The "odds" of keeping the particles stable once they are below 200 nm in size is 7 out of 14[2] (50%). Therefore, the "odds" just to get to a stable dispersion having a particle size less than 200 nm is (14/18)*(7/14) = 39%.

With this in mind, one of ordinary skill in the art would now consider the likelihood of obtaining a sterile filterable dispersion from the stable dispersions having a particle size of less than 200 nm. As noted above, the "odds" of this event is 6 out of 7 (86%). Thus, realizing that one of ordinary skill in the art would consider all the events that would direct him to the claimed invention, the "odds" of successfully obtaining a stable nanoparticulate dispersion having a particle size of less than 200 nm that is sterile filterable is (14/18)*(7/14)*(6/7) = 33%, a 1 in 3 chance. Such "odds" do not reflect a high predictability of obtaining a successful result.

Considering the Examples in Applicants' specification show the "odds" of predictability are 1 in 3, one of ordinary skill in the art would not reach the same conclusion as the Examiner: that Desai can be read as a general teaching that as long as the particles in a dispersion are smaller than 0.2 μm, they can be sterilized by filtration.

Finally, Example 15 clearly demonstrates that a nanoparticulate dispersion having a particle size of 99 nm cannot pass through a 0.2 micron filter. It is improper for the Examiner simply dismisses this evidence with an allegation that the data is "unexplainable" in the absence of any data or rationale supplied by the Examiner.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the

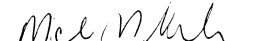
[2] Those Examples that were unsuccessfully milled to particles sizes below 200 nm (Examples 7, 9, 12 and 14) are removed from the analysis pool.

undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Oct 29, 2008

By 

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